The Interface

Cholesterol Quandaries: Relationship to Depression and the Suicidal Experience

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked. In this edition of The Interface, we examine the relationship between low serum cholesterol and mood disorders.

INTRODUCTION

A number of investigators have found a possible relationship between low serum cholesterol levels and mood disorders. In addition, low serum cholesterol levels have been associated with suicidal ideation and suicide attempts. While the pathophysiology of this association remains unknown, some researchers have postulated that there may be a relationship between altered lipid metabolism and changes in serotonin functioning. In addition, some researchers have found that the pharmacological treatment of depression results in increased serum cholesterol levels. While controversies and inconsistencies characterize this area of study, it appears reasonable to conclude the following: (a) alterations in lipid metabolism may be one of several risk factors for the subsequent development of depression and/or suicidal ideation/suicide attempts (i.e., a non-specific contributory variable) and/or (b) low serum cholesterol levels are an inconsistent but possible biological marker for the manifestation of these phenomena in some individuals.[1]

LOW CHOLESTEROL AND DEPRESSION

A number of studies in various types of populations have found an association between low serum cholesterol levels and depressive symptoms and/or mood disorders.

General population studies. In a Finnish community sample of nearly 30,000 participants, investigators found that low serum cholesterol levels were associated with depressed mood and a heightened risk of hospitalization for depression.[2]

Outpatient samples. In addition to general population studies, the relationship between low serum cholesterol levels and depression has been explored in outpatient samples. For example, in an Irish study of primary care patients, Rafter found that participants with low serum cholesterol levels scored significantly higher on depression assessments.[3]

Inpatient samples. A relationship between low serum cholesterol levels and depressed mood has also been examined among various types of psychiatric inpatient samples. For example, in an Italian study, Borgherini and

colleagues found that lower serum cholesterol levels correlated with higher scores on the depression assessment that was used in this study.[4] In a US study, Ghaemi and colleagues examined consecutive admissions to an affective disorders unit and found, compared with the bipolar subsample, lower cholesterol levels among those with unipolar depression.[5] Glueck and colleagues examined hospitalized patients with affective disorders and, in comparison with controls, found a relationship between low serum cholesterol levels and affective disorders.[6] These findings have been replicated in other studies, as well.[7–9]

Cholesterol and depression in special populations. In addition to the association between low serum cholesterol levels and depressive symptoms/mood disorders in community and general patient samples, investigators have examined this relationship in somewhat unique types of populations. For example, Pjrek and colleagues confirmed this relationship in a controlled study of patients with seasonal affective disorder.[10] Dimopoulos and colleagues substantiated this relationship in a sample of elderly Greek patients.[11] Their findings among elderly patients were echoed in a sample of Finnish males[12] as well as a US sample of patients over the age of 70 years.[13] A relationship between low serum cholesterol and depressive symptoms has also been found among women during the post-partum period.[14–16]

Studies with negative findings. While a substantial number of studies indicate an association between low serum cholesterol levels and depressive symptoms and diagnoses, not all studies have found support for such a relationship. For example, in a nonclinical sample of Japanese males, investigators found that higher serum cholesterol levels were associated with depression.[17] Negative findings have been reported in several other clinical studies of depressed individuals as well.[18–25] To augment the preceding findings, among a large retrospective sample of patients suffering from affective psychoses, Fritze and colleagues found no association between low serum cholesterol levels and depressive symptoms.[26] Findings have also been negative in several studies of post-partum women.[27,28]

Glueck and colleagues examined hospitalized patients with affective disorders and, in comparison with controls, found a relationship between low serum cholesterol levels and affective disorders.[6] These findings have been replicated in other studies, as well.[7–9]

LOW CHOLESTEROL AND SUICIDAL IDEATION/SUICIDE ATTEMPTS/PARASUICIDE

Cholesterol and suicidal ideation. In addition to studies on the relationship between cholesterol and depressive symptoms/disorders, investigators have also examined the relationship between low serum cholesterol levels and suicidal ideation. For example, in a controlled study from South Korea, Kim and Myint examined depressed patients admitted to an emergency department and developed subsamples according to the presence or not of suicidal ideation.[29] Compared to those without such ideation, those with suicidal ideation evidenced lower serum cholesterol levels. These findings were replicated in a Polish study by Rabe-Jablonska and Poprawska, in which low serum cholesterol levels statistically correlated with suicidal ideation.[30]

Cholesterol and suicide attempts. In addition to suicidal ideation, low serum cholesterol levels have been associated with bonafide suicide attempts. For example, in a controlled study from the UK, Kunugi and colleagues examined patients who were admitted from the emergency department following a suicide attempt; compared with non-attempting psychiatric inpatients and normal controls, those with suicide attempts evidenced lower serum cholesterol levels.[31] Sarchiapone and colleagues examined patients who were admitted to hospital following an intentional overdose.[32] Compared with controls, the cohort of patients' status-post overdose had significantly lower serum cholesterol levels. In an Israeli sample, Modai and colleagues found that compared with non-suicidal depressed patients, suicide attempters evidenced significantly lower serum cholesterol levels.[33]

In keeping with these data, researchers from New Zealand examined the relationship between low serum cholesterol levels and the degree of the suicidal process. Using three levels of status (i.e., no suicidal thoughts, suicidal thoughts, suicide attempt), Sullivan and colleagues found that there was a significant association

between lower serum cholesterol levels and increasing degrees of suicidal experience.[34]

Finally, Garland and colleagues examined cholesterol abnormalities among a consecutive sample of patients with self-harm behavior, but not genuine suicide attempts (i.e., parasuicidal patients). In this population, investigators also found a significantly lower mean serum cholesterol level.[35]

Studies with negative findings. As expected, several studies have found no association between low serum cholesterol levels and suicidal ideation.[20,26] There are also studies that indicate no relationship between low serum cholesterol levels and bonafide suicide attempts[36–40] or parasuicidal behavior.[41] Finally, among a cohort of schizophrenic patients, there was no association between low serum cholesterol levels and completed suicide.[42]

INTERPRETATION OF AVAILABLE DATA

Given these conflicting data, we suggest the following tentative conclusions. Despite the noted inconsistencies in empirical findings, there are a substantial number of studies that support a relationship between low serum cholesterol levels and depressive symptoms/disorders and suicidal ideation/suicide attempts. In affected individuals, this relationship appears most often to be an inverse one (i.e., that low serum cholesterol levels correlate with these various psychiatric phenomena). That the relationship is an inconsistent one does not necessarily imply that it is an invalid one. Rather, the inconsistency suggests that the relationship is probably a variable or a partial one (i.e., low serum cholesterol levels variably or partially contribute to or manifest with these psychiatric phenomena) that may only be relevant in some individuals. Given the role of variable or partial contribution, whether this relationship is genuinely causal (i.e., that low serum cholesterol levels contribute to the generation of psychopathology) or secondary (psychopathology results in low serum cholesterol levels) remains unknown.

PATHOPHYSIOLOGY

If low serum cholesterol levels are genuinely associated with the described psychopathologies, what might be the pathophysiology of such a relationship? The pragmatic answer is that no one knows. Papakostas and colleagues offer some in-depth and complex hypotheses that might explain the relationship between low serum cholesterol levels and the discussed psychopathologies.[43] These explanations relate to cholesterol levels in cell membranes, inhibited neuronal growth, and attenuated serotonergic function. Other authors discuss the possible roles of serotonin transporters,[44] decreased serotonin receptors,[45] inter-relationships with leptin,[46] dietary intake,[47] decreased serotonin turnover,[48] interleukin-2,[49] and genetics.[50] Given the plethora of tentative possibilities, there is likely to be a very complex and/or an elusive psychobiological interface.

MEDICATIONS AND EFFECTS ON CHOLESTEROL

Given that the preceding data is inconsistent, we suggest that the relationship between low serum cholesterol and depressive symptoms/disorders and suicidal ideation/attempts is not a strictly predictable one. Rather, it appears to be only partially and moderately specific. Given this tentative conclusion, is there any evidence that medications can cause simultaneous changes in serum cholesterol levels and mood?

Cholesterol-lowering medications and psychopathology. As expected, the literature on the psychiatric effects of cholesterol-lowering medications is controversial. For example, Boston, Dursun, and Reveley indicate that there is substantial evidence that lowering cholesterol levels with medications is associated with an increase in various psychiatric disorders (e.g., depression) and violent deaths—findings that emerged in cardiovascular primary prevention studies.[51] However, other investigators indicate that no such relationship is evident in their empirical studies.[52,53]

Psychotropic medications and cholesterol effects. In samples of depressed patients, several studies indicate that effective mood-disorder treatment results in an increase in serum cholesterol levels. These findings

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have been reported with various antidepressants and mood stabilizers,[54] doxepin,[55] imipramine,[56] paroxetine,[57] and even following treatment with electroconvulsive therapy.[58] However, in future studies, the explicit duration of drug treatment as well as weight status throughout the study of participants would have to be meticulously clarified.

predisposition to depressive symptoms/mood disorders and suicidal ideation/suicide attempts that is presaged by low serum cholesterol levels; whether cholesterol assessment, in conjunction with the measurement of other metabolic or neurohormonal parameters, might suffice as a biological marker in some susceptible individuals; and whether in affected individuals, cholesterol elevation with treatment signifies a consistently good response to medications. Only further investigation will clarify these intriguing cholesterol quandaries.

...future investigations need to examine whether some individuals have a predisposition to depressive symptoms/mood disorders and suicidal ideation/suicide attempts that is presaged by low serum cholesterol levels; whether cholesterol assessment, in conjunction with the measurement of other metabolic or neurohormonal parameters, might suffice as a biological marker in some susceptible individuals; and whether in affected individuals, cholesterol elevation with treatment signifies a consistently good response to medications.

As expected, there are also studies indicating that antidepressant treatment does not affect cholesterol levels. For example, there is a six-week study of trazodone[59] and a six-month study of bupropion—both with negative findings.[60]

CONCLUSIONS

Given the inconsistencies in the data, it appears that only some individuals with low serum cholesterol levels evidence depressive symptoms, mood disorders, suicidal ideation, and/or suicide attempts. Whether this metabolic peculiarity is causal or secondary to these psychopathologies is unknown. In addition, we do not know if this particular subgroup consistently responds to antidepressant treatment with an elevation in serum cholesterol levels. However, this area of investigation appears potentially fertile. Indeed, future investigations need to examine whether some individuals have a

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INVEGA®

(paliperidone) Extended-Release Tablets

Brief Summary

BEFORE PRESCRIBING INVEGA®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these subjects revealed a risk of death in the drug-treated subjects of between 1.6 to 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. INVEGA® (paliperidone) Extended-Release Tablets is not approved for the treatment of patients with Dementia-Related Psychosis. *[see Warnings and Precautions]*

INVEGA® (paliperidone) Extended-Release Tablets are indicated for the acute and maintenance treatment of schizophrenia *[see Clinical Studies]*.

CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. INVEGA® (paliperidone) is a metabolite of risperidone and is therefore contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in INVEGA®.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. INVEGA® (paliperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients With Dementia-Related Psychosis: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA® was not marketed at the time these studies were performed. INVEGA® is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning]*.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA® (C_{max} ss = 113 ng/mL and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which C_{max} ss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study.

For the three fixed-dose efficacy studies, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the INVEGA® 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). No subject receiving INVEGA® had a QTcLD exceeding 500 msec at any time in any of these three studies.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA® was not marketed at the time these studies were performed, it is not known if INVEGA® is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperprolactinemia: Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Potential for Gastrointestinal Obstruction: Because the INVEGA® tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA® should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA® should only be used in patients who are able to swallow the tablet whole *[see Dosage and Administration]*.

A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal

neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract.

Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Potential for Cognitive and Motor Impairment: Somnolence and sedation were reported in subjects treated with INVEGA® *[see Adverse Reactions]*. Antipsychotics, including INVEGA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures: During premarketing clinical trials (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) and 0.25% of subjects treated with placebo. Like other antipsychotic drugs, INVEGA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for INVEGA® should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Priapism: Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA®, paliperidone shares this pharmacologic activity and, therefore, may be associated with this risk. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): No cases of TTP were observed during clinical studies with paliperidone. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA® to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic Effect: An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Use in Patients with Concomitant Illness: Clinical experience with INVEGA® in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology]*.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

INVEGA® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA®, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions]*.

Monitoring: Laboratory Tests: No specific laboratory tests are recommended.

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions]*
- QT prolongation *[see Warnings and Precautions]*
- Tardive dyskinesia *[see Warnings and Precautions]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions]*
- Hyperprolactinemia *[see Warnings and Precautions]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions]*
- Seizures *[see Warnings and Precautions]*
- Dysphagia *[see Warnings and Precautions]*
- Suicide *[see Warnings and Precautions]*
- Priapism *[see Warnings and Precautions]*
- Thrombotic thrombocytopenic purpura (TTP) *[see Warnings and Precautions]*
- Disruption of body temperature regulation *[see Warnings and Precautions]*
- Antiemetic effect *[see Warnings and Precautions]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions]*

The most common adverse reactions in clinical trials (reported in 5% or more of subjects treated with INVEGA® and at least twice the placebo rate in any of the dose groups) were akathisia and extrapyramidal disorder.

The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in 2% of INVEGA®-treated subjects) were nervous system disorders *[see Adverse Reactions]*.

The safety of INVEGA® was evaluated in 1205 adult subjects with schizophrenia who participated in three placebo-controlled, 6-week, double-blind trials, of whom 850 subjects received INVEGA® at fixed doses ranging from 3 mg to 12 mg once daily. The information presented in this section was derived from pooled data from these three trials. Additional safety information from the placebo-controlled phase of the long-term maintenance study, in which subjects received INVEGA® at daily doses within the range of 3 mg to 15 mg (n=104), is also included.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of INVEGA® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for INVEGA® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials: *Table 1* enumerates the pooled incidences of adverse reactions reported in the three placebo-controlled, 6-week, fixed-dose studies, listing those that occurred in 2% or more of subjects treated with INVEGA® in any of the dose groups, and for which the incidence in INVEGA®-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo.

Table 1. Adverse Reactions in Short-Term, Fixed-Dose, Placebo-Controlled Trials in Adult Subjects with Schizophrenia*: Body System or Organ Class (Dictionary-derived Term) **Percent of Patients Reporting Event Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth, **Total percentage of subjects with adverse reactions** 37, 48, 47, 54, 60; **Cardiac disorders:** Atrioventricular block first degree 1, 2, 0, 2, 1; Bundle branch block 2, 3, 1, 3, <1; Sinus arrhythmia 0, 2, 1, 1, <1; Tachycardia 7, 14, 12, 12, 14; **Gastrointestinal disorders:** Abdominal pain upper 1, 1, 3, 2, 2; Dry mouth 1, 2, 3, 1, 3; Salivary hypersecretion <1, 0, <1, 1, 4; **General disorders:** Asthenia 1, 2, <1, 2, 2; Fatigue 1, 2, 1, 2, 2; **Nervous system disorders:** Akathisia 4, 4, 3, 8, 10; Dizziness 4, 6, 5, 4, 5; Dystonia 1, 1, 1, 5, 4; Extrapyramidal disorder 2, 5, 2, 7, 7; Headache 12, 11, 12, 14, 14; Hypertonia 1, 2, 1, 4, 3; Parkinsonism 0, 0, <1, 2, 1; Somnolence 7, 6, 9, 10, 11; Tremor 3, 3, 3, 4, 3; **Vascular disorders:** Orthostatic hypotension 1, 2, 1, 2, 4. * Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA® dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from three studies; one study included once-daily INVEGA® doses of 3 mg and 9 mg, the second study included 6 mg, 9 mg, and 12 mg, and the third study included 6 mg and 12 mg *[see Clinical Studies]*. Adverse reactions for which the INVEGA® incidence was equal to or less than placebo are not listed in the table, but included the following: vomiting.

Less Commonly-Observed Adverse Reactions: The following list contains all serious and non-serious adverse reactions reported at any time by individuals taking INVEGA® during any phase of a trial within the premarketing database (n = 2720), except (1) those listed in *Table 1* above or elsewhere in labeling, (2) those for which a causal relationship to INVEGA® use was considered remote, and (3) those occurring in only one subject treated with INVEGA® and that were not acutely life-threatening. **Cardiac disorders:** bradycardia, palpitations **Gastrointestinal disorders:** abdominal pain, swollen tongue **General disorders:** edema **Immune system disorders:** anaphylactic reaction **Vascular disorders:** ischemia

Discontinuations Due to Adverse Reactions: The percentages of subjects who discontinued due to adverse reactions in the three placebo-controlled, 6-week, fixed-dose studies were 3% and 1% in INVEGA®- and placebo-treated subjects, respectively. The most common reasons for discontinuation were nervous system disorders (2% and 0% in INVEGA®- and placebo-treated subjects, respectively).

Dose-Related Adverse Reactions: Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with INVEGA®, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, Parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

Demographic Differences: An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies did not reveal any evidence of differences in safety on the basis of gender or race alone; there was also no difference on the basis of age *[see Use in Specific Populations]*.

Extrapyramidal Symptoms (EPS): Pooled data from the three placebo-controlled, 6-week, fixed-dose studies provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS (*Table 2*), and (4) incidence of spontaneous reports of EPS (*Table 3*). For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA® 3 mg and 6 mg doses for any of these EPS measures.

Table 2. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication: EPS Group Percentage of Patients Placebo (N=355) first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth, Parkinsonism [a] 9, 11, 3, 15, 14; Akathisia [b] 6, 6, 4, 7, 9; Use of anticholinergic medications [c] 10, 10, 9, 22, 22. a: For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items) b: For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2 c: Percent of patients who received anticholinergic medications to treat emergent EPS

Table 3. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term: EPS Group Percentage of Patients Placebo (N=355) first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth, Overall percentage of patients with EPS-related AE 11, 13, 10, 25, 26; Dyskinesia 3, 5, 3, 8, 9; Dystonia 1, 1, 1, 5, 5; Hyperkinesia 4, 4, 3, 8, 10; Parkinsonism 2, 3, 3, 7, 6; Tremor 3, 3, 3, 4, 3; Dyskinesia group includes: Dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia Dystonia group includes: Dystonia, muscle spasms, oculogyration, trismus Hyperkinesia group includes: Akathisia, hyperkinesia Parkinsonism group includes: Bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism Tremor group includes: Tremor

Laboratory Test Abnormalities: In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, a between-group comparison revealed no medically important differences between INVEGA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® was associated with increases in serum prolactin *[see Warnings and Precautions]*.

Weight Gain: In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were compared, revealing a similar incidence of weight gain for INVEGA® 3 mg and 6 mg (7% and 6%, respectively) compared with placebo (5%), and a higher incidence of weight gain for INVEGA® 9 mg and 12 mg (9% and 9%, respectively).

Other Findings Observed During Clinical Trials: The safety of INVEGA® was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA® in adults with schizophrenia *[see Clinical Studies]*. In general, adverse reaction types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse reactions reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase.

Adverse Reactions Reported With Risperidone: Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

DRUG INTERACTIONS

Potential for INVEGA® to Affect Other Drugs: Given the primary CNS effects of paliperidone *[see Adverse Reactions]*, INVEGA® should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA® is administered with other therapeutic agents that have this potential *[see Warnings and Precautions]*.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein. Paliperidone is therefore not expected to inhibit P-glycoprotein-mediated transport of other drugs in a clinically relevant manner.

Potential for Other Drugs to Affect INVEGA®: Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance.

Paliperidone is metabolized to a limited extent by CYP2D6 *[see Clinical Pharmacology]*. In an interaction study in healthy subjects in which a single 3 mg dose of INVEGA® was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: There are no adequate and well controlled studies of INVEGA® in pregnant women. INVEGA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated during the period of organogenesis with up to 8 times the maximum recommended human dose of paliperidone (on a mg/m^2 basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, there were increases in pup deaths seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see risperidone package insert).

Labor and Delivery: The effect of INVEGA® on labor and delivery in humans is unknown.

Nursing Mothers: Paliperidone is 9-hydroxyrisperidone, the active metabolite of risperidone. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Caution should be exercised when INVEGA® is administered to a nursing woman. The known benefits of breastfeeding should be weighed against the unknown risks of infant exposure to paliperidone.

Pediatric Use: Safety and effectiveness of INVEGA® in patients < 18 years of age have not been established.

Geriatric Use: The safety, tolerability, and efficacy of INVEGA® were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received flexible doses of INVEGA® (3 mg to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA® (3 mg to 15 mg once daily) *[see Clinical Studies]*.

Overall, of the total number of subjects in clinical studies of INVEGA® (n = 1796), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment *[see Clinical Pharmacology]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration]*.

Renal Impairment: Dosing must be individualized according to the patient's renal function status *[see Dosage and Administration]*.

Hepatic Impairment: No dosage adjustment is required in patients with mild to moderate hepatic impairment. INVEGA® has not been studied in patients with severe hepatic impairment.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe INVEGA®.

Orthostatic Hypotension: Patients should be advised that there is risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions]*.

Interference with Cognitive and Motor Performance: As INVEGA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA® therapy does not affect them adversely *[see Warnings and Precautions]*.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with INVEGA® *[see Use in Specific Populations]*.

Nursing: Caution should be exercised when INVEGA® is administered to a nursing woman. The known benefits of breastfeeding should be weighed against the unknown risks of infant exposure to paliperidone. *[See Use in Specific Populations]*.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions *[see Drug Interactions]*.

Alcohol: Patients should be advised to avoid alcohol while taking INVEGA® *[see Drug Interactions]*.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions]*.

Administration: Patients should be informed that INVEGA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool *[see Dosage and Administration]*.

INVEGA® (paliperidone) Extended-Release Tablets

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